Allopurinol, erythema multiforme, and renal insufficiency

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Allopurinol should be prescribed judiciously in the presence of renal insufficiency, in reduced dosage, but where possible is best avoided

Allopurinol, a xanthine oxidase inhibitor, has become established as the drug of choice for preventing and treating conditions where there is overproduction of uric acid, such as occurs in gout, uric acid nephrolithiasis, and polycythaemia vera; during chemotherapy for lymphomas; and in the Lesch-Nyhan syndrome.[1] Allopurinol may, however, cause a severe, and sometimes fatal, hypersensitivity reaction in patients with pre-existing renal disease. We describe two patients with severe hypersensitivity. In both the syndrome was relapsing and in one ultimately fatal.

Case 1

A 52 year old man presented with a five day history of a widespread rash, oral and genital ulceration, fever, malaise, diarrhoea, and diminished urine output. Five weeks earlier he had developed gout in his great toe, for which he was treated with ibuprofen followed by allopurinol 300 mg daily. Then his serum urate concentration was 0·78 mmol/l (normal $<0·42$) and serum creatinine concentration 130 μmol/l (normal <110). Idiopathic dilated cardiomyopathy had been diagnosed three years previously. He had taken warfarin, enalapril, and frusemide regularly since then and, intermittently, ibuprofen for episodic back pain.

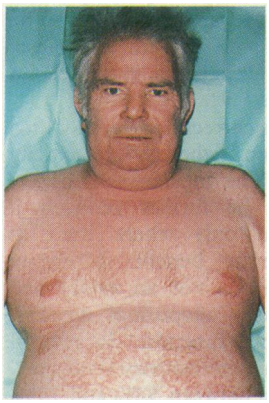

Fig 1—*Case 1. Widespread morbilliform rash. (Reproduced with the patient's permission)*

On examination he was feverish and unwell. His face was red and oedematous, and he had blistering on his hands and feet, superficial ulceration in the mouth and conjunctiva, and balanitis. He had a morbilliform rash over his trunk and limbs (fig 1). Blood pressure was 80/50 mm Hg and urine output 20 ml/h. There was haematoproteinuria but no urinary casts. The white cell count was 17×10^9/l with 70% neutrophils and 12% eosinophils. Erythrocyte sedimentation rate was 85 mm in 1 h, alanine aminotransferase concentration was 143 U/l (normal <31), and the creatinine concentration had risen to 360 μmol/l. The kidneys were anatomically normal with good perfusion but had impaired function as assessed by ultrasound and isotope scans. Skin biopsy was consistent with a diagnosis of erythema multiforme (fig 2) but serial antistreptolysin O, *Herpes simplex*, and *Mycoplasma* titres were normal. IgE levels were raised at 480 IU/l (2 to 120). Blood, throat swab, and urine cultures were sterile. The monospot test for infectious mononucleosis and tests for syphilis were negative. Antinuclear and anticardiolipin antibody titres were normal, as were levels of complement and rheumatoid factor. Echocardiography excluded infective endocarditis.

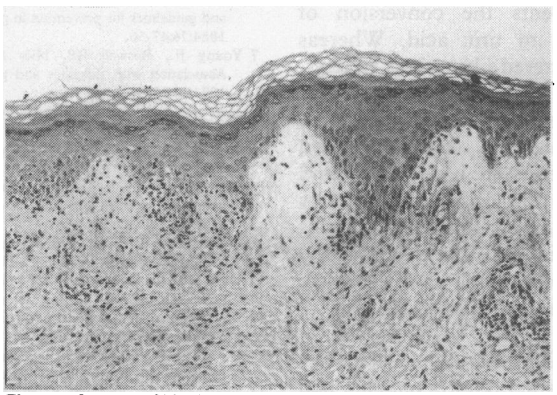

Fig 2—*Case 1. Skin biopsy specimen showing a blistering eruption. Blisters have an intact roof and contain fibrin and segmented leucocytes. In the dermis, which is superficially oedematous, there is a mixed inflammatory cell infiltrate that is also seen around vessels (haematoxylin and eosin×150)*

All his drugs were stopped when he was admitted to hospital. In addition to rehydration and inotropes he received cefotaxime and metronidazole for three days pending culture results. He showed no signs of improvement until he was given methylprednisolone 0·5 g intravenously: within six hours his temperature had returned to normal and the cutaneous oedema began to subside. He was continued on oral prednisolone 1 mg/kg daily. In 10 days his rash faded without exfoliation, and at two weeks the serum creatinine concentration had returned to its pre-illness level.

He suffered minor relapses with a recrudescence of the rash on each occasion at one, three, and five months when prednisolone was reduced below 15 mg. Subsequently azathioprine was added, and on a dosage of 50 mg daily his steroid requirement fell to 7·5 mg. Fifteen months after his initial presentation he was well on long term immunosuppressant therapy.

Case 2

A 78 year old man started treatment with allopurinol 300 mg daily for asymptomatic hyperuricaemia. Four weeks later he developed a generalised pruritic rash associated with oral ulceration and facial swelling. He had previously been taking ibuprofen for arthritis and atenolol for hypertension for many years.

On examination he was feverish and his face was erythematous and swollen. He had superficial oral ulcers, and on his trunk and limbs there was a morbilliform eruption. Urine showed red cells and a trace of protein. The haemoglobin concentration was 118 g/l, white cell count $10·3\times10^9$/l with 70% neutrophils and 14% eosinophils, platelets 128×10^9/l, and erythrocyte sedimentation rate 55 mm in 1 h. His urea concentration was 44·8 mmol/l, creatinine concentration 524 μmol/l, and urate concentration 0·63 mmol/l. Mild renal insufficiency had been noted in 1986 (urea 9·6 mmol/l, creatinine 135 μmol/l). Liver function tests (alanine aminotransferase and alkaline phosphatase) and clotting studies gave only slightly abnormal results. IgE values were raised at 320 IU/l. The following investigations were normal: throat swab, urine and blood culture, complement levels, autoantibodies, antistreptolysin O titre, viral and atypical antibody titres including *Herpes simplex* and *Mycoplasma*, and hepatitis and syphilis serology.

Features of a drug reaction consistent with an erythema multiforme type picture were evident on skin biopsy. Kidney biopsy showed two pictures: a granulomatous interstitial nephritis in keeping with a hypersensitivity drug reaction (fig 3) and IgM mesangioproliferative glomerulonephritis, which is the likely explanation for the patient's pre-existing renal impairment.

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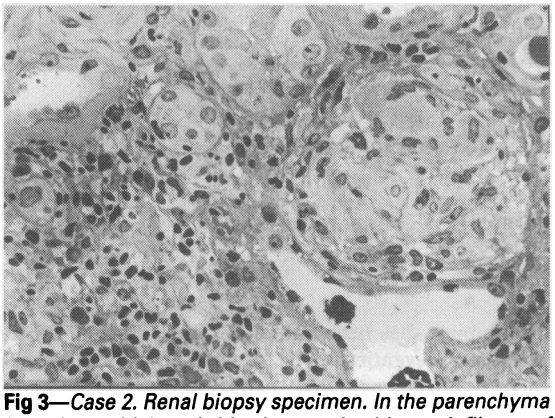

Fig 3—*Case 2. Renal biopsy specimen. In the parenchyma is an interstitial nephritis characterised by an infiltrate of plasma cells and eosinophils, and a single epithelioid cell granuloma. Adjacent tubules show non-specific changes (haematoxylin and eosin×600)*

The patient responded slowly to treatment with prednisolone 40 mg daily in addition to topical steroid and emollients, which provided symptomatic relief. During the course of the next three months, his serum creatinine concentration settled at 190 μmol/l, urine analysis no longer showed blood or protein, and by six months steroids had been tapered to 5 mg. Shortly after this he died from a severe, systemic vasculitis which was manifest as a recurrence of his cutaneous reaction, bloody diarrhoea, vasculitic lesions on his toes, and rapidly worsening renal function.

Discussion

Allopurinol is generally considered to be a safe and well tolerated drug.[1 2] Whereas minor, self limiting reactions such as itch, rash, and bowel upset occur in up to 10% of patients taking the drug, severe adverse effects are rare.[3 4] Nevertheless, patients with renal insufficiency, or those taking a thiazide diuretic together with allopurinol, have a substantially increased risk of developing a potentially life threatening hypersensitivity reaction.[5 6] The allopurinol hypersensitivity syndrome is characterised by fever, eosinophilia, hepatitis, renal failure, and a skin eruption which may take the form of erythema multiforme, Stevens-Johnson syndrome or, in the worst cases, toxic epidermal necrolysis. The average time of onset of the syndrome after starting allopurinol is two to six weeks but can be considerably longer, and mortality is upwards of 20%.[5 6] The underlying disease is often, but not invariably, a diffuse vasculitis induced by a type III hypersensitivity reaction probably triggered by oxipurinol, allopurinol's principal metabolite.[6-8] Oxipurinol inhibits xanthine oxidase by binding tightly to it and so prevents the conversion of hypoxanthine and xanthine to uric acid. Whereas allopurinol is rapidly excreted by the kidneys, oxipurinol, which is actively reabsorbed by the renal tubules, has a long elimination half life of 14-26 hours.[6] Oxipurinol therefore accumulates in renal failure, and raised serum levels of the metabolite have been found to correlate with risk of developing the toxicity syndrome.[1 6] Furthermore, since thiazide diuretics cause retention of uric acid and may impair the clearance of oxipurinol, patients taking both a thiazide diuretic and allopurinol are at increased risk of developing hypersensitivity.[9]

In over 80% of cases of allopurinol hypersensitivity syndrome described in published reports patients had evidence of renal impairment before they started allopurinol, and in most no reduction in the standard dose of allopurinol of 300 mg was made.[5] Renal function declines steadily with age but loss of function is not always reflected by a rise in serum creatinine concentration.[10] Thus, the elderly are most vulnerable to developing hypersensitivity reactions. Estimation of allopurinol requirement should be based on creatinine clearance (see table), but may be approximated as follows[11]:

$$\text{Creatinine clearance (ml/min)} = \frac{1{\cdot}2 \times (140 - \text{age in years}) \times \text{weight in kg}}{\text{Serum creatinine in } \mu\text{mol/l}}$$

This is the formula for men. For women the same formula can be used, but the result should be multiplied by 0·85.

In both the cases reported here the pretreatment renal insufficiency was more severe than the serum creatinine concentration suggested. Their estimated creatinine clearances were 50 ml/min (case 1) and 30 ml/min.

Management relies on early recognition of the problem and withdrawal of allopurinol. If intervention is delayed renal failure often progresses and dialysis is required.[12 13] The pattern of the kidney lesion is variable, and acute interstitial nephritis,[14 15] focal segmental glomerulonephritis,[7] and vasculitis[8 16] have all been described. Secondary skin infection is common and contributes to mortality. In addition to supportive treatment, most advocate steroids,[9 17] especially in the presence of multisystem disease, and these need to be maintained for long periods to prevent a relapse. Relapse occurred in both of our patients, in the second with disastrous consequences.

If allopurinol is given in the correct dosage, modified with respect to renal function,[1 6] then severe toxicity reactions are seldom seen. The incidence of hypersensitivity reactions would be further reduced if allopurinol were prescribed only where there is clear evidence of therapeutic benefit. Moderate asymptomatic hyperuricaemia is not an established indication for treatment with allopurinol since it confers no protection of renal function.[1] In reviews considering the allopurinol hypersensitivity syndrome, a high proportion of patients, between 52% and 75%, were receiving the drug for symptomless hyperuricaemia.[5 6 9] In these cases the elimination of contributing factors such as alcohol, drugs, and diet would probably have sufficed and prevented considerable morbidity.[2]

Maintenance dose of allopurinol in renal insufficiency (after Hande et al[6])

Creatinine clearance (ml/min)	Allopurinol dose
0	100 mg every 3 days
10	100 mg every 2 days
20	100 mg daily
40	150 mg daily
60	200 mg daily
⩾100	300 mg daily

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